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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brent R. Stockwell et al.	Art Unit:	1639
Serial No.:	09/611,835	Examiner:	My-Chau T. Tran
Filed:	July 7, 2000	Customer No.:	21559
Title:	METHODS FOR IDENTIFYING COMBINATIONS OF ENTITIES AS THERAPEUTICS		

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Applicant's Brief on Appeal

In accordance with Applicants' Notice of Appeal received by the Patent and Trademark Office on September 23, 2005, Applicants submit this Brief on Appeal.

This Brief is accompanied by the fee set forth in § 41.20 (b)(2), as well as a Request for Extension of Time, to and including March 23, 2006. Appended hereto are a Claims Appendix and a Related Proceedings Appendix.

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Real Party in Interest

The real party in interest is CombinatoRx, Inc., the sole assignee of the above-captioned application.

Related Appeals and Interferences

There are no pending appeals or interferences related to this case.

Status of Claims

All of the pending claims, claims 89-156, have been finally rejected under 35 U.S.C. § 103 (a) over a single reference, Stylli et al. U.S. Patent No. 5,985,214 ("Stylli"). The rejection of all claims is appealed.

Status of Amendments

No amendments have been filed subsequent to the final rejection.

Summary of Claimed Subject Matter

Five independent claims are pending; these are summarized below, with references provided to the relevant portions of the specification. The claims, although of different scope in certain respects, share a common feature—they are directed to large-scale screening of combinations of compounds to identify combinations having biological activity indicative of their potential utility as therapeutics.

Claim 89

Claim 89 is directed to a screening method; the method is used for discovering combinations of compounds with therapeutic utility. The method tests large numbers (at least forty-nine combinations of at least seven compounds) for the ability to affect a biological property in test cells. As is described in the specification (pp. 34-37), at the time the application was filed, the method had succeeded in identifying several biologically active compound combinations. It has also been made of record in the case (in a personal Interview and in the subsequent Reply), a drug combination identified using the method of claim 89, chlorpromazine and pentamiadine, both FDA-approved drugs, has shown promise for treating cancer in an FDA-approved clinical study. The invention of claim 89 is described in the specification on page 4, lines 18-27.

Claim 114

Claim 114 is directed to a screening method that shares features of cliam 89. Claim 114, like claim 89, screens combinations of compounds against cells. Claim 114 requires a higher number of combinations: at least two hundred unique combinations of at least seven compounds. The invention of claim 114 is described in the specification on page 5, lines 1-9.

Claim 135

Claim 135 is directed to a screening method that also shares features with claim 89. Claim 135 adds a rapid-screening limitation: the claim requires that the screening of different pairs (or greater) of compounds be screened at least 25 times over a one-week period. The invention of claim 135 is described in the specification on page 5, lines 15-24.

Claim 149

Claim 149 is directed to a screening method which, like the method of claim 89, identifies therapeutically effective combinations of compounds. Claim 149 requires testing of a higher number of combinations—at least ten thousand—and requires testing that large number of compounds at least twice over a period of ten days or less. The invention of claim 149 is described in the specification on page 6, lines 10-20, and page 4, line 20.

Claim 154

Claim 154, like the other claims, is directed to a combination screening method. Claim 154 recites a first step not present in the other independent claims: before combinations are tested, at least 100 compounds are tested individually for activity against test cells. Compounds that demonstrate activity individually are then tested as

large numbers of combinations. The invention of claim 154 is described in the specification on page 6, lines 21-27 through page 7, lines 1-6.

Grounds of Rejection to be Reviewed on Appeal

All of the claims were rejected for obviousness over the Stylli reference. The Examiner (referring to claim 89), while admitting that Stylli "does not expressly disclose that the chemical compounds tested are forty-nine unique combinations of seven different compounds," argues that Stylli does "hint at the claimed inventive concept of multi-compound screening, i.e., screening a desired two or higher order combination of compounds."

In support of this assertion, the Examiner quotes a single sentence from Stylli: "[I]n practicing the methods of the invention, the products or compositions can be used alone or in combination with one another or in combination with other therapeutic or diagnostic agents." The Examiner (misreading the sentence) asserts that it constitutes a teaching of "screening a combination of compounds (see e.g. col. 44, lines 20-23)."

Thus, all sixty-seven claims of the present application stand finally rejected for obviousness based on a single mis-read sentence of one reference.

Argument

I. Rejection of Claims 89-108; 110; 112-129; 131; 133-145; 147; 149; 150; and 152

These claims, like the other pending claims, were rejected for obviousness over Stylli.

As is discussed above, all of the claims listed in this Section I require screening of large numbers of combinations of compounds against test cells for biological activity. Thus, if the only reference cited in the final Office Action were totally unrelated to screening combinations of compounds for biological activity, the rejection would necessarily constitute unambiguous, reversible error, with no additional showing or argument necessary. In fact, that is the case. Stylli does not teach or suggest screening combinations of compounds.

As is mentioned above, the Examiner rests the obviousness rejection on a single sentence of Stylli, an issued patent containing sixty-two columns of text, almost all of which is devoted to describing an automated system for identifying individual compounds having biological activity. That this is Stylli's subject is evident even from the patent's title: "Systems and Methods for Rapidly Identifying Useful Chemicals in Liquid Samples." Stylli thus is one member of the ranks of hundreds or perhaps thousands of references describing automated systems for identifying individual active compounds. Stylli, like all of those others, is not relevant to the patentability of the present claims, all of which require screening of large numbers of combinations of compounds.

The Examiner does not assert that the teachings of Stylli regarding the screening of individual compounds are relevant to the patentability of the present claims. Rather, the Examiner relies on a misreading of a single sentence in Stylli, quoted above and presented again below: "[I]n practicing the methods of the invention, the products or compositions can be used alone or in combination with one another or in combination with other therapeutic or diagnostic agents."

The quoted sentence from Stylli does not say what the Examiner says it does—that drug combinations should be screened. This is not a question of interpretation; the meaning of the sentence is entirely clear. In that sentence, following the subject "products or compositions," is a verb, "used." The verb "to use" is not a synonym for "to screen." The verb means "employed." The products of Stylli are, according to the cited sentence, "used," or employed, for some purpose, and that purpose is absolutely clear: therapy. The sentence is referring to combination therapy, the administration of a combination of drugs to a person, and not to combination screening. The "methods of the invention" referred to in the passage are methods of treatment, not methods of screening.

If further evidence of the obvious, incontrovertible fact that Stylli is referring only to combination therapy, not combination screening, were required, the context of the cited sentence provides such evidence. The title of the section of Stylli in which the cited sentence appears is "Pharmaceutical Compositions" (column 43, line 45; emphasis added). The next thirteen paragraphs provide descriptions of various pharmaceutical compositions, dosages, and routes of administration. Indeed, the sentence preceding the

one quoted by the Examiner is directed to factors associated with dosing, which pertains only to therapy, not screening.

This clear, unambiguous error by the Examiner necessitates reversal.

II. Rejection of Claims 109; 111; 130; 132; 146; 151; and 153

These claims, which are all dependent claims, were rejected for obviousness over Stylli. Because these claims depend from claims requiring screening of large numbers of compounds, they necessarily contain that feature. Therefore, like the claims from which they depend, they are patentable over Stylli for the reasons given in Part I above, which reasons are hereby incorporated by reference.

The claims listed in Part II also recite a significant limitation not recited in the other claims: they all require that at least one of the compounds being screened be an FDA-approved drug. As is explained in the specification (p.8, line 26-27 through p. 9, lines 1-2), where the compounds in successful combinations are already FDA-approved , "the new combination has the further advantage of being easily moved through the FDA-approval process." I.e., using FDA-approved drugs greatly reduces the time and money required to have a combination approved for marketing. Screening of FDA-approved drugs is the antithesis of most references, including Stylli, whose purpose is discovering biologically active molecules which themselves were previously unknown, or whose activity was previously unknown. Stylli certainly has nothing to do with compounds whose activity was previously known, let alone recognized as such by the FDA. Indeed,

Stylli explicitly states that the described invention was made in order "to identify chemicals with useful activity" (col. 1, lines 54-5; emphasis added).

III. Rejection of Claims 154-156

These claims were rejected for obviousness over Stylli. Claim 154 is independent; claims 155 and 156 depend from claim 154.

Claims 154-156, like all of the other claims, require screening of large numbers of combinations of compounds, and therefore they are patentable over Stylli for the reasons given in Part I above, which reasons are hereby incorporated by reference.

In addition, as is discussed above, claim 154 recites a first step not present in the other independent claims: before combinations are tested, at least 100 compounds are tested individually for activity against test cells. Compounds that demonstrate activity individually are then tested as large numbers of combinations.

Advantages of the method of claim 154 are discussed in the specification on p. 28, lines 1-8:

> Activity Rank-Order Screen
>
> A diverse library may initially be tested individually using standard methodologies. The compounds are screened in a biological assay and ranked by activity. The most active compounds (e.g., the twenty most active or the thousand most active, depending on the amount of combinatorial space to be assayed) in the library are then tested pair-wise and in three-way combinations. If desired, these combinations can be again ranked by activity and the process iterated for four-way combinations, five-way combinations, etc., until a desired number of effective combinations are identified.

Thus, a greater level of efficiency can be provided, as the least active compounds are excluded so that they are never combined for screening. Certainly nothing in Stylli suggests the additional feature of testing compounds individually prior to testing combinations, nor does the Examiner cite any passage of Stylli purporting to suggest this feature.

Conclusion

For all of the reasons given above, it is respectfully requested that the final rejection of all of the claims be reversed. Enclosed is a check for $250.00 in payment of the fee required by 37 C.F.R. § 41.20(b)(2). If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 13 2006

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Claims Appendix

89. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:

(a) providing at least forty-nine unique combinations of at least seven different compounds,

(b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,

(c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,

(d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal, and

(e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells.

90. The method of claim 89, wherein step (b) comprises sequentially contacting said combinations of compounds with said test cells.

91. The method of claim 89, wherein said detecting step (c) is performed by a cytoblot assay.

92. The method of claim 89, wherein said detecting step (c) is performed by a reporter gene assay.

93. The method of claim 89, wherein said detecting step (c) is performed by a fluorescence resonance energy transfer assay.

94. The method of claim 89, wherein said detecting step (c) is performed by detecting a fluorescent calcium-binding indicator dye.

95. The method of claim 89, wherein said detecting step (c) employs fluorescence microscopy.

96. The method of claim 89, wherein step (c) employs expression profiling.

97. The method of claim 89, wherein said cells are human cells.

98. The method of claim 89, wherein said cells are selected from the group consisting of cancer cells, immune cells, neurons, fibroblasts, bacterial cells, and fungal cells.

99. The method of claim 89, wherein step (b) is carried out using a robotics system.

100. The method of claim 89, wherein step (b) is carried out using microfluidics.

101. The method of claim 89, wherein step (b) is carried out using ink-jet printer technology.

102. The method of claim 89, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

103. The method of claim 89, wherein at least one of said compounds is employed in purified form.

104. The method of claim 103, wherein each of said compounds is employed in purified form.

105. The method of claim 89, wherein said compounds are provided as components of mixtures.

106. The method of claim 105, wherein said mixtures are natural product extracts.

107. The method of claim 89, wherein said effect is a synergistic effect.

108. The method of claim 89, wherein at least one of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

109. The method of claim 108, wherein said molecule is an FDA-approved drug.

110. The method of claim 108, wherein each of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

111. The method of claim 110, wherein said each of said compounds are FDA-approved drugs.

112. The method of claim 89, wherein each of said combinations screened for biological activity is a two-compound combination.

113. The method of claim 89, wherein each of said combinations screened for biological activity is a three-compound combination.

114. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:

(a) providing at least two hundred unique combinations of at least seven different compounds,

(b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,

(c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,

(d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal, and

(e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells.

115. The method of claim 114, wherein step (b) comprises sequentially contacting said compounds with said test cells.

116. The method of claim 114, further comprising the step of (f) repeating step (a) through (e) at least twice, wherein, in step (b), said contacting of at least 200 combinations is different in each repetition.

117. The method of claim 116, wherein at least two repetitions of step (f) occur within 10 days of each other.

118. The method of claim 114, wherein said contacting step (b) comprises contacting at least 400 unique two or higher order combinations of compounds and said compounds individually with living test cells.

119. The method of claim 114, wherein said contacting step (b) comprises contacting at least 1540 unique two or higher order combinations of compounds and said compounds individually with living test cells.

120. The method of claim 114, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

121. The method of claim 114, wherein at least one of said compounds is employed in purified form.

122. The method of claim 114, wherein each of said compounds is employed in purified form.

123. The method of claim 114, wherein said compounds are provided as components of mixtures.

124. The method of claim 123, wherein said mixtures are natural product extracts.

125. The method of claim 114, wherein said effect is a synergistic effect.

126. The method of claim 114, wherein step (b) is carried out using a robotics system.

127. The method of claim 114, wherein step (b) is carried out using microfluidics.

128. The method of claim 114, wherein step (b) is carried out using ink-jet printer technology.

129. The method of claim 114, wherein at least one of said compounds is a molecule with a molecular weight of less than 1500 g/mole..

130. The method of claim 129, wherein said molecule is an FDA-approved drug.

131. The method of claim 129, wherein each of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

132. The method of claim 131, wherein said small compounds are FDA-approved drugs.

133. The method of claim 114, wherein each of said combinations screened for biological activity is a two-compound combination.

134. The method of claim 114, wherein each of said combinations screened for biological activity is a three-compound combination.

135. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:

(a) providing at least forty-nine unique combinations of at least seven different compounds,

(b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,

(c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,

(d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal,

(e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is greater than the effect of each compound, individually, on said biological property of the test cells, and

(f) repeating steps (a) through (e) at least 25 times over a one-week period, using different combinations of compounds in each repetition.

136. The method of claim 135, wherein steps (a) through (e) are repeated at least 100 times over a 30-day period, using different combinations of compounds in each repetition.

137. The method of claim 135, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

138. The method of claim 135, wherein said compounds are employed in purified form.

139. The method of claim 135, wherein said compounds are provided as components of mixtures.

140. The method of claim 139, wherein said mixtures are natural product extracts.

141. The method of claim 135, wherein said effect is a synergistic effect.

142. The method of claim 135, wherein step (b) is carried out using a robotics system.

143. The method of claim 135, wherein step (b) is carried out using microfluidics.

144. The method of claim 135, wherein step (b) is carried out using ink-jet printer technology.

145. The method of claim 135, wherein at least one of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

146. The method of claim 145, wherein said molecule is an FDA-approved drug.

147. The method of claim 145, wherein each of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

148. The method of claim 147, wherein said compounds are FDA-approved drugs.

149. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:

(a) providing at least ten thousand unique combinations of ~~at least seven different~~ compounds,

(b) contacting each unique combination with living test cells under conditions that ensure that each contacting is segregated from the others,

(c) measuring or detecting said biological property of the test cells as an indication of the effect of each combination on the test cells,

(d) identifying combinations of compounds that have an effect on a property of the test cells that is indicative of the potential for therapeutic efficacy in an animal,

(e) at any time during said method, contacting each compound in the combination identified in step (d) with said living test cells and thereafter measuring or detecting said biological property of the test cells as an indication of the effect of each compound on the test cells, wherein the combination identified in step (d) constitutes said desired combination if the effect of the combination on said biological property of the test cells is

greater than the effect of each compound, individually, on said biological property of the test cells, and

(f) repeating steps (a) through (e) at least twice over a period of ten days or less, wherein, in step (a), said step of providing at least ten thousand unique combinations of at least seven different compounds is different in two or more repetitions.

150. The method of claim 149, wherein at least one of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

151. The method of claim 150, wherein said molecule is an FDA-approved drug.

152. The method of claim 150, wherein each of said compounds is a molecule with a molecular weight of less than 1500 g/mole.

153. The method of claim 152, wherein said compounds are FDA-approved drugs.

154. A method of discovering a desired two or higher order combination of compounds having the ability to affect a biological property of living cells in a way that is indicative of the potential for therapeutic efficacy in an animal, said method comprising the steps of:

(a) contacting living test cells with at least 100 compounds under conditions that ensure that each compound/test cell contacting is segregated from the others,

(b) detecting or measuring a biological property of said test cells,

(c) selecting compounds that cause a change in said biological property relative to said biological property of said test cells not contacted with said compounds,

(d) contacting at least 49 unique two or higher order combinations of the selected compounds of step (c) with living test cells under conditions that ensure that each

contacting is segregated from the others,

(e) detecting or measuring a biological property of said test cells of step (d), and

(f) identifying combinations of compounds that cause an effect on said biological property of said test cells that is different from the effect of each compound of the combination by itself, wherein said identified combinations of compounds have potential therapeutic use in an animal.

155. The method of claim 154, wherein the test cells of step (a) are the same as the test cells of step (d).

156. The method of claim 154, wherein the biological property of step (b) is the same as the biological property of step (d).

Related Proceedings Appendix

There are no related proceedings.

Evidence Appendix

None.